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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

516,423

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
100708-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE 2003/000857	27.05.2003	31.05.2002
International Patent Classification (IPC) or national classification and IPC		
A61K 9/00, A61K 31/397, A61P 9/00		
Applicant		
AstraZeneca AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☒ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.12.2003	23.09.2004
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE 2003/000857

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))
☐ publication of the international application (under Rule 12.4)
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 11

because:

☒ the said international application, or the said claims Nos. 11 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-10	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-10	NO
Industrial applicability (IA)	Claims	1-10	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The following documents were cited in the International Search Report:

D1: US 6034104 A
D2: WO 0013671 A1
D3: WO 0018352 A2
D4: WO 0214270 A1
D5: WO 0042059 A1
D6: WO 9927913 A1
D7: WO 9739770 A1

The problem the present application aims to solve is to provide an immediate release pharmaceutical formulation comprising a compound of formula (I) as defined in the application.

The scope of the present invention is very broad and comprises, with only three exceptions, every imaginable immediate release formulation comprising the compounds of formula (I). The claims actually formulate the problem, which the present invention aims to solve, rather than a solution to this problem. The examination relates to immediate release formulations comprising compounds of formula (I) in general. The opinion has however been focused on formulations similar to those exemplified in the application.

The description discloses a multitude of excipients that may be used in the formulations of the invention and provides examples of a large variety of formulations. In this way the application provides several completely different solutions to

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

the problem of providing an immediate release pharmaceutical formulation comprising a compound of formula (I).

Different types of immediate release formulation have been examined although the opinion is focused on formulations similar to those presented in the examples.

The document D1 presents several examples (column 16, line 16-column 18, line 18) of formulations comprising thrombin inhibitors which are structurally very similar to the compounds of the present invention. The examples show different types of formulation which should give immediate release whereof some are similar to the formulations of the present invention.

D2 discloses solid immediate release formulations comprising thrombin inhibitor resembling those of the present invention (page 3, lines 8-14). The formulations contain, for example, cellulose and starch. Example 1 shows a formulation which, apart from the active agent, has the same ingredients as the compositions of examples 44-47, 76 and 78 of the present invention.

D3 relates to a preparation comprising a thrombin inhibitor and/or an NSAID. Several examples of formulations which seem to provide immediate release and which resemble the formulations of the present application are disclosed.

D4 and D5 describe compounds which are structurally very similar to the compounds of the present invention. The documents disclose a solution of active agent and water, a solution of active agent and dimethylsulphoxide and a solution of ethanol, solutol and water (5:5:90). These compositions correspond to the compositions excluded from the scope of the present invention with the only difference being that the active ingredient is slightly different.

To prepare any immediate release formulation of a novel pharmaceutical agent is not considered to be an invention as such but rather a problem to be solved. There are several immediate release formulations known in the art which, by a person skilled in the art, easily can be adapted to novel

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

substances. From D1-D5 immediate release formulations comprising active agents similar to those of the present invention and with compositions similar to those of the examples of the present application are known. Considering what is known from D1-D5 and other prior art it is considered to lie within the skills of a person skilled in the art to prepare immediate release formulations comprising compounds of formula (I).

Compounds structurally similar to the active compounds of the invention are known from, for example, D4 and D5 for use as anticoagulant agents. It is therefore considered to be obvious to a person skilled in the art to use the compounds of formula (I) in the treatment of cardiovascular disorders.

The invention according to claims 1-10 is according to the reasoning above considered to lack inventive step. In order to prove that the subject matter of the application is inventive the formulation should be properly defined by its actual composition and limited to a single invention for which there is support in the description and an unexpected effect compared to similar compositions known in the art should be shown.
Thus, the claimed invention is considered to be novel and has industrial applicability but lacks inventive step.

D6 and D7 describe the general state of the art and have not been considered when establishing the opinion of this statement.

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Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
WO 0244145 A1	06.06.2002	30.11.2001	01.12.2000

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The scope of the present invention is very broad and comprises, with only three exceptions, every imaginable immediate release formulation comprising the compounds of formula (I). The claims do not explain in any way how such immediate release formulations may be achieved. The formulation is defined by a desirable characteristic, namely that it should give immediate release of the active ingredient, and not by its actual composition. The claims actually formulate the problem, which the present invention aims to solve, rather than a solution to this problem. Due to this the claims are not considered to fulfil the demands of clarity as stated in Article 6 PCT. The examination relates to immediate release formulations comprising compounds of formula (I) in general. The opinion has however been focused on formulations similar to those exemplified in the application.

The description discloses a multitude of excipients that may be used in the formulations of the invention and provides examples of a large variety of formulations. In this way the application provides several completely different solutions to the problem of providing an immediate release pharmaceutical formulation comprising a compound of formula (I). On the other hand the problem of preparing for example, a solution for injection is completely different from the problem of preparing for example a tablet for oral administration. The application can in this way be considered to provide solutions to several different problems.

According to Rule 13 PCT the application shall relate to one invention only or a group of inventions linked by a single general inventive concept. Independently of whether the application is considered to provide different solutions to the same problem or to solve different problems, such a general inventive concept linking all the different types of immediate release formulations, can not be found in the present application. The present application may therefore be considered to include several independent inventions. It is, however, impossible to define a number of specific invention. Again, different types of immediate release formulation have been examined although the opinion is focused on formulations similar to those presented in the examples.